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Modulation of noradrenergic neurotransmission by prejunctional auto- and heteroreceptors in the freely moving rat

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Summary

Prejunctional receptors modulating noradrenaline release from sympathetic nerves have been studied extensively during the last two decades. Most evidence supporting a modulatory role for these receptors has been obtained from studies using isolated tissues, *in situ* perfused organs, pithed animals or anaesthetized animals. In this thesis two different models were used to study the *in vivo* function and capacity of prejunctional auto- and heteroreceptors modulating endogenous noradrenaline overflow in the vasculature of freely moving rats.

Firstly, the local modulation of electrically evoked noradrenaline overflow through prejunctional receptors in the portal vein was studied. For this purpose Wistar rats were permanently instrumented with a bipolar stimulation electrode around the vein, located between two cannulas, one for the infusion of drugs (upstream) and one for the sampling of blood, placed downstream of the first cannula. Biphasic pulses of 2 Hz, 3 msec and 5 mA were used to stimulate the nervous plexus of the portal vein to elicit the release of noradrenaline. Infusion of drugs through the infusion cannula allowed the local application of drugs modulating the electrically evoked noradrenaline overflow. In some studies, an additional cannula was inserted in the abdominal aorta, enabling simultaneous measurement of blood pressure and heart rate (chapters 2-6).

Secondly, the physiological role of prejunctional receptors modulating exercise-induced overflow of noradrenaline was studied. The rats used in this study were permanently instrumented with a sampling cannula placed in the right jugular vein and an infusion cannula in the left jugular vein. Swimming exercise, a physiological way of activating the sympathetic nervous system, was used to elicit the release of noradrenaline. The rats were forced to swim against a counter current for 20 minutes, while blood samples were taken to establish changes in noradrenaline levels. Adrenodemedullated animals were used to prevent adrenaline release from the adrenal medulla to interfere with the prejunctional receptors studied (chapter 7 and 8).

The capacity of angiotensin II as a hormonal modulator activating prejunctional receptors facilitating noradrenaline overflow was studied in **chapter 2**. Local infusion in the portal vein of angiotensin II (0.1, 0.5 and 1 $\mu\text{g/kg/min}$) induced a pronounced increase of both basal and electrically evoked noradrenaline overflow (upto 213% and 209%, respectively). The angiotensin II receptor antagonist saralasin (10 $\mu\text{g/kg/min}$) completely reversed these effects, showing the presence of facilitatory prejunctional angiotensin II receptors. Angiotensin II has also been proposed to act as a local transjunctional modulator of noradrenaline release. Postjunctional activation of β_2 -adrenoceptors has been suggested to activate the local vascular formation and release of angiotensin II. Since both the β_2 -adrenoceptor agonist fenoterol (0.25 mg/kg) and angiotensin II induced a strong facilitation of the electrically evoked noradrenaline overflow, part of the effect of fenoterol might be due to the mechanism described above. Inhibition of angiotensin II synthesis using captopril (10 mg/kg) or blockade of prejunctional angiotensin II receptors using saralasin, however, did not change the facilitation of both basal and electrically evoked noradrenaline overflow induced by fenoterol, indicating no transjunctional modulatory role of angiotensin II in the β_2 -adrenoceptor facilitated noradrenaline release in the portal vein.

On the other hand postjunctional receptor activation by fenoterol and angiotensin II, however, did induce marked changes in mean arterial pressure. Changes in blood pressure induce a baroreceptor reflex mediated alteration in sympathetic nerve activation which will lead to changes in heart rate and plasma noradrenaline independent of prejunctional receptors (**chapter 3**). To study the possible interference of the baroreceptor reflex on the prejunctional effects of fenoterol and angiotensin II, the effects of the vasodilator sodium nitroprusside (2.5 $\mu\text{g/kg/min}$) and the vasoconstrictor phenylephrine (2.5 $\mu\text{g/kg/min}$), which are both devoid of a prejunctional action, were studied. Both compounds did not change the *electrically* evoked noradrenaline overflow, showing that the facilitation of evoked overflow by fenoterol and angiotensin II, is solely due to local prejunctional β_2 -adrenergic and angiotensin II receptors. The enhancement of basal noradrenaline concentration, which is derived from numerous peripheral sympathetic junctions, by fenoterol and angiotensin II, however, is strengthened or dampened, respectively, by baroreceptor reflex-mediated changes in sympathetic nerve activity.

The influence of the co-transmitter neuropeptide Y (NPY), known as a co-transmitter of noradrenaline, on electrically evoked noradrenaline overflow was studied in **chapter 4**. Infusion of NPY (2-2000 ng/kg/min) showed that prejunctional NPY receptors are able to inhibit almost completely the electrically evoked noradrenaline overflow. Infusion of the Y_1 -selective agonist [Leu³¹,Pro³⁴]NPY and the Y_2 -selective agonist NPY-(18-36), suggested a prejunctional heterogeneity of both Y_1 and Y_2 receptors. [Leu³¹,Pro³⁴]NPY even showed a biphasic inhibition pattern. It was suggested that the potent inhibition of evoked noradrenaline overflow by NPY is due to a concerted activation of both Y_1 and Y_2 receptors.

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The subsequent 4 chapters discuss the role of adrenaline as a co-transmitter of noradrenaline. Infusion of 100 ng/min adrenaline for two hours in adrenalectomized rats, followed by an interval of one hour, in which the plasma adrenaline concentration returned to undetectable levels, resulted in an enhancement of electrically evoked noradrenaline of 194% of control (saline infusion). Furthermore adrenaline was also released, together with noradrenaline, resulting in total catecholamine overflow upto 258% of control (**chapter 5**). This facilitatory effect of adrenaline on the electrically evoked overflow is mediated through prejunctional β_2 -adrenoceptors since it could be blocked by the selective β_2 -adrenoceptor antagonist ICI 118,551 (0.3 mg/kg). The neuronal uptake blocker cocaine (2.5 mg/kg plus 0.05 mg/kg/min) infused together with adrenaline prevented the evoked release of adrenaline as well as facilitation of the evoked overflow, revealing the neuronal origin of the adrenaline released. α_2 -Autoreceptor blockade with yohimbine (0.5 mg/kg) after adrenaline infusion further augmented the evoked overflow of noradrenaline plus adrenaline. It was concluded that adrenaline can be taken up by sympathetic nerve terminals via cocaine sensitive uptake carriers and is released during nerve stimulation to facilitate neurotransmitter overflow through activation of prejunctional β_2 -receptors.

Two different doses of adrenaline (20 and 100 ng/min) were used in **chapter 6** to study the duration of the facilitatory effects of co-released adrenaline. Both doses of adrenaline enhanced electrically evoked noradrenaline overflow to the same extent, indicating the involvement of inhibitory prejunctional α_2 -autoreceptors at the highest dose used. Repeated stimulation after 24 h, 48 h and 72 h showed that co-released adrenaline from sympathetic nerve terminals is able to facilitate noradrenaline overflow upto 48 hours after administration. These effects could be blocked by ICI 118,551 (0.3 mg/kg) showing again the involvement of prejunctional β_2 -adrenoceptors.

The effect of exogenously applied adrenaline (100 ng/min, administered as in chapters 5 and 6), taken up and released from sympathetic nerves, on the swimming exercise induced noradrenaline overflow in adrenalectomized Wistar rats was studied in **chapter 7**. As during electrical stimulation, swimming exercise induces the release of adrenaline after preloading. During the first 3 min of swimming the overflow of noradrenaline and adrenaline was enhanced to 178% of control (saline infusion). During the whole 20 minutes of swimming exercise, the enhancement of the overflow of both catecholamines was slightly less (upto 165%). Cocaine, in the same dose as above, again blocked the uptake and release of adrenaline as well as its facilitatory effect. Yohimbine (0.25 mg/kg) further enhanced the facilitatory effect of co-released adrenaline which could be blocked by ICI 118,551 (1.0 mg/kg). The results showed that also during a physiological activation of the sympathetic nervous system, like swimming exercise, adrenaline can be released as a co-transmitter and is able to markedly facilitate the noradrenaline (and adrenaline) overflow through prejunctional β_2 -adrenoceptors.

In **chapter 8** the role of adrenaline and the occurrence of prejunctional receptor alterations in the development of hypertension in the spontaneously hypertensive rat (SHR) were studied using the same experimental protocol as in chapter 7. The SHR is a widely used model of human essential hypertension. Hypertension starts to develop in these animals from the 4th week of age on. Adrenodemedullation at this age was shown to attenuate the development of hypertension. SHR demedullated at 4 weeks of age (SHR-ADM4) responded to swimming exercise very similar as normotensive adrenodemedullated Wistar rats (WRADM), both after saline and after adrenaline (100 ng/min) infusion. However, SHR, adrenodemedullated at 16 weeks (SHR-ADM16) had enhanced responsiveness, resulting in a strongly elevated exercise induced noradrenaline (and adrenaline) overflow, indicating that adrenaline plays an important role in the genesis of this form of genetic hypertension as far as sympathetic neurotransmission is involved. The relative contribution of the prejunctional β_2 -adrenoceptor mediated enhancement of noradrenaline overflow by co-released adrenaline during swimming, however, was similar in all rats studied. Administration of yohimbine (0.25 mg/kg) revealed that in SHR-ADM16, in contrast to SHR-ADM4 and normotensive Wistar rats, inhibitory α_2 -adrenoceptors were partially defective, resulting in enhanced noradrenaline and adrenaline overflow during exercise, particularly during the first 3 minutes of swimming. The results indicate that adrenaline may play an important role in the initiation of hypertension at a critical stage of enhanced β_2 -adrenoceptor responsiveness in young prehypertensive SHR, whereas subsensitive prejunctional α_2 -adrenoceptors may play a role in the maintenance of hypertension.

In conclusion, both models of local and general noradrenaline overflow used in this thesis have proven very useful in the study of the physiological function of prejunctional receptors modulating endogenous noradrenaline overflow *in vivo*. Locally released co-transmitters, like NPY and adrenaline, probably play an important role in the modulating of noradrenaline release and consequently in the regulation of local vascular tension and eventually in the regulation of blood pressure.